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Expert Review of Hematology

ISSN: 1747-4086 (Print) 1747-4094 (Online) Journal homepage: http://www.tandfonline.com/loi/ierr20

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To cite this article: Mario Tiribelli , Gianni Binotto & Massimiliano Bonifacio (2017): The significance of early warning in chronic myeloid leukemia, Expert Review of Hematology, DOI: 10.1080/17474086.2017.1340715

To link to this article: http://dx.doi.org/10.1080/17474086.2017.1340715

Accepted author version posted online: 09 Jun 2017.
Published online: 15 Jun 2017.

EXPERT REVIEW OF HEMATOLOGY, 2017
https://doi.org/10.1080/17474086.2017.1340715

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LETTER TO THE EDITOR

The significance of early warning in chronic myeloid leukemia

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Dear Editor:

We have read with great interest the manuscript by Eskazan and colleagues entitled 'Critical appraisal of European LeukemiaNet (ELN) 2013 recommendations for the management of chronic myeloid leukemia: is it early for a warning?' [1]. After a revision of the relatively limited literature, the authors conclude that there are still no solid data to suggest a switch of therapy in patients with warning signs and that long-term survival remains a highly significant endpoint in CML patients. While we generally agree with these thoughts, we would like to stress a couple of additional points on the issue of ELN 2013 – defined 'warning'.

The ELN recommendations defines warning as less than partial cytogenetic response (PCyR) and/or BCR-ABL1 > 10% (according to the International Scale – IS) at 3 months, less than complete cytogenetic response (CCyR) and/or BCR-ABL 1 > $1\%^{IS}$ at 6 months, and BCR-ABL1 > 0.1% ^{IS}, i.e. no major molecular response (MMR), at 12 months [2]. So, at the first two time-points, conventionally considered as 'early' [3], both cytogenetic and molecular status define response, while at 12 months only BCR-ABL1 level > 0.1 to $1\%^{IS}$ identifies warning patients, as anything less than CCyR is regarded as a failure. Our group analyzed the outcome of 216 CML patients treated with front-line standard dose (400 mg/day) imatinib with discordant cytogenetic and molecular responses at 3 and 6 months [4]. Patients with even a single warning sign at 3 months (i.e. no PCyR or BCR-ABL1 > $10\%^{IS}$) had a significantly lower chance to obtain a subsequent CCyR (37% compared to 85% in patients with concordant optimal cytogenetic and molecular responses) and worse failure-free survival (FFS) (39% vs. 81% at 48 months). Similarly, a warning sign at 6 months identified patients less prone to attain a MMR at 12 months (17% vs. 82% in concordantly optimal patients) and with worse FFS (62% vs. 88%) [4].

In our experience, most discordant patients had a 'molecular warning', as 15/17 discordant at 3 months were in PCyR or better but with BCR-ABL1 transcript > $10\%^{IS}$ and at 6 months 20/25 discordant were in CCyR with BCR-ABL1 > $1\%^{IS}$. This finding is an indirect confirmation of the importance of a BCR-ABL1 transcript level < $10\%^{IS}$ at 3 months (now defined 'early molecular response' [EMR]) as a positive predictor of long-term outcome, as reported by different studies [5,6]. Despite EMR is gaining ground as a factor for an early switch of therapy, as suggested by NCCN guidelines [7], some reports indicate, in line with ELN recommendations, to consider also the 6-month cytogenetic or molecular status to assess a two-point evaluation of response to tyrosine kinase inhibitor (TKI) therapy. The MDACC group analyzed the outcome of 453 CML patients treated with different TKIs, finding that 19 out of 44 patients (43%) not achieving major (i.e. optimal) cytogenetic response (MCyR) at 3 months obtained this response at 6 months and had an outcome comparable to patients achieving an earlier MCyR [8]. A Canadian study reviewed 320 patients receiving imatinib therapy with 3- and 6-month BCR-ABL1 transcript levels available, reporting that patients not achieving an EMR at 3 months but with BCR-ABL1 transcript < 1% at 6 months ($n = 18$) had similar FFS, progression-free survival (PFS), and overall survival (OS) compared to patients in EMR ($n = 184$) [9]. Taken together, these data suggest that cytogenetic and molecular response at 6 months can identify a subgroup with favorable outcome among patients 'warning' at 3 months. However, considering patients with cytogenetic and/or molecular warning at 3 months in our series ($n = 41$), only 2 had a subsequent optimal cytogenetic and molecular response at 6 months (unpublished). Moreover, we found that the rates of warning responses at 3 and 6 months were higher in cases with b2a2 BCR-ABL1 transcript type compared to those with b3a2 variant (32% vs. 24% at 3 months and 31% vs. 12% at 6 months, respectively) [10].

If there is still debate on the practical significance of a warning at 3 or 6 months, even less consensus and significantly less data are about the meaning of a late (i.e. at 12 months) warning. Starting from their database of 483 patients treated with four different TKI strategies, colleagues at MDACC found no benefit, in term of survival, in patients achieving MMR while in CCyR, even if their landmark analysis was performed at 18 and 24 months, and not at the 12-month time-point [11]. A landmark analysis of PFS and OS on the bases of molecular response at 12 months of imatinib performed in 128 patients from our database did not find any difference between patients in MMR or not (unpublished). Concordantly, a Spanish group showed that, in 198 patients treated with standard-dose imatinib and in CCyR without MMR at 12 months, a switch to a second-generation TKI was associated with a higher probability of subsequently major and deep molecular response, but no advantage in terms of PFS and OS and

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higher rates of discontinuation for adverse events, compared to patients continuing imatinib [12].

Hopefully, more information on the therapeutic approach to 'warning' patients will come from an upcoming study of the GIMEMA Working Party on CML study aimed to evaluate efficacy of nilotinib frontline versus imatinib followed by switch to nilotinib in the case of absence of ELN-defined optimal response at 3, 6, or 12 months [13].

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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